Of the fit and the fat: mitochondrial abnormalities and type 2 diabetes mellitus

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Editorial: Of the Fit and the Fat: Mitochondrial Abnormalities and Type 2 Diabetes Mellitus

Due to our current lifestyle, characterized by low levels of physical activity and an overconsumption of energy-rich foods, we are now facing a dramatic worldwide increase in the prevalence of obesity and type 2 diabetes mellitus (1). One of the earliest hallmarks of type 2 diabetes is the resistance of peripheral tissues, such as skeletal muscle and liver, toward the action of the hormone insulin, leading to a reduced removal of blood glucose from the circulation. Much research has been devoted toward unraveling the causal factors leading to insulin resistance. For skeletal muscle, this has led to the suggestion that the accumulation of triglyceride—and its intermediates—is causally related to the development of insulin resistance. Indeed, both type 2 diabetic patients (2) and first-degree relatives of these patients, who have an increased risk to develop diabetes (3, 4), are characterized by increased levels of intramuscular triglycerides. Moreover, the acute elevation of circulating plasma fatty acids induces muscular insulin resistance after 2–3 h, paralleled by an elevation of intramuscular triglycerides (5, 6). Can we conclude from these findings that intramuscular fat accumulation is detrimental to muscular insulin sensitivity? The negative answer to this question can be deduced from the finding that endurance-trained athletes, who are highly insulin sensitive, are also characterized by elevated levels of intramuscular triglycerides (2). In exercising humans, intramuscular triglycerides may actually be essential to fuel the mitochondria with substrate sources for the formation of ATP needed for muscle contraction. Considering this, intramuscular triglyceride stores may even have been indispensable from an evolutionary perspective because it has been hypothesized that humans evolved into highly capable endurance runners when compared with most other species, and that this running capability may have been instrumental in the evolution of the human body form (7). However, in our modern society, the need to run long distances has rapidly vanished, but the capability to store fat inside muscle cells has not. As a result, the human body can store excessive energy not only in the white adipose tissue, but also in nonadipose tissues such as skeletal muscle.

If intramuscular triglycerides *per se* are not detrimental to muscular insulin resistance, what then is the role of these fat stores in the etiology of insulin resistance? A major metabolic difference between endurance-trained athletes and type 2 diabetic patients is the oxidative capacity of the skeletal muscle. This has led to the suggestion that actually the intermediates of muscular triglyceride metabolism may interfere with insulin signaling: if a high intramuscular triglyceride content is not accompanied by a high capacity to oxidize (or reesterify) this intramuscular fat, intermediates of triglyceride metabolism, such as fatty acyl-coenzyme A or diacylglycerol, may accumulate, whereas these intermediates remain low when oxidative capacity is high. Together, this suggests that oxidative capacity may well be a more important factor in the etiology of type 2 diabetes mellitus. In line with this, it was recently shown that despite similar levels of intramuscular triglycerides, only type 2 diabetic patients were characterized by a reduced *in vivo* mitochondrial function when compared with age- and body mass index-matched obese controls (8). This finding does not stand alone; in the last 5 yr, a reduced mitochondrial function has been postulated to be a causal factor in the etiology of type 2 diabetes mellitus. Using noninvasive magnetic resonance spectroscopy, a reduction in ATP synthesis rate accompanied by higher intramyocellular lipid levels was shown in first-degree relatives of type 2 diabetes mellitus patients (9). In addition, two independent studies showed a coordinated reduction of genes encoding key enzymes in oxidative metabolism and mitochondrial function, which are under the control of the peroxisome proliferator-activated receptor-γ coactivator (PGC1), in human type 2 diabetes (10, 11). Furthermore, aberrations in mitochondrial morphology, *i.e.* smaller and damaged mitochondria, were reported in type 2 diabetic patients (12). Jointly, these studies hint toward abnormalities in mitochondrial function and/or oxidative capacity, and the prevailing hypothesis states that this may lead to the accumulation of fat and its intermediates in skeletal muscle, ultimately leading to insulin resistance and type 2 diabetes mellitus. Alternatively, it has been suggested that mitochondrial dysfunction may in fact be the consequence of elevated triglyceride levels in skeletal muscle (13, 14).

Notwithstanding the recent findings that favor a major role of mitochondrial dysfunction in (obesity-induced) type 2 diabetes, several important questions remain to be answered. In the current issue of this journal, Heilbronn *et al.* (15) investigated one of these remaining questions, *i.e.* the influence of fatness and fitness on markers of mitochondrial metabolism. A reduced mitochondrial function as reported in (pre-)diabetes may simply be the result of a more inactive lifestyle in these subjects, and many of the previous studies did not account for this confounding factor. Heilbronn *et al.* (15) here used an approach in which sedentary, nondiabetic but overweight/obese male subjects were divided into insulin-sensitive and insulin-resistant groups, based on the median glucose infusion rate determined using a hyperinsulinemic euglycemic clamp. All subjects were selected to be inactive, and importantly the two groups were indeed similar with regard to VO_2max, a marker of aerobic fitness, as well as for age, body mass index (and body fat percentage),

Abbreviations: PGC1, Peroxisome proliferator-activated receptor-γ coactivator; UCP3, uncoupling protein-3.

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and fasting glucose levels. The authors found that the mRNA levels of PGC1α, cytochrome oxidase subunit 1, and uncoupling protein-3 (UCP3) were significantly lower in insulin-resistant subjects. UCP3 is a mitochondrial protein that may be involved in the protection of mitochondria against lipid-induced oxidative mitochondrial damage. Therefore, a reduced UCP3 content in insulin-resistant subjects could indicate that the mitochondria in these subjects are less well protected against lipid-induced damage, which could ultimately lead to mitochondrial damage (16). PGC1α is a transcriptional coactivator involved in mitochondrial biogenesis (the new formation of mitochondria). Consistent with its reduction, protein levels of complexes I and III of the mitochondrial electron transport chain and citrate synthase activity were significantly lower in insulin-resistant subjects. Remarkably, no differences in intramyocellular lipid or fatty acyl-coenzyme A levels were observed between the insulin-resistant and insulin-sensitive groups, which may suggest that other fatty acid intermediates like diacylglycerol may be more closely related to insulin resistance.

What can we learn from these results? At first glance, the results seem to stress further the importance of mitochondrial aberrations in the etiology of type 2 diabetes mellitus. The fact that aerobic fitness was similar between the groups suggests that the mitochondrial abnormalities found in the insulin-resistant groups were not simply due to a more sedentary lifestyle, but could really reflect an inherited defect of insulin-resistant subjects. Alternatively, however, the data can be interpreted as the mitochondrial aberrations being the result of the insulin resistance. In that respect, skeletal muscle mitochondrial function and gene transcription were recently compared in type 2 diabetic patients and nondiabetic controls at artificially maintained low or high insulin levels (17). It was found that in type 2 diabetic patients, high insulin levels reduced the expression of PGC1α, citrate synthase, and cytochrome oxidase subunit 1 and blunted the insulin-stimulated increase in mitochondrial ATP production. Of interest, in the insulin-resistant group of the study of Heilbronn *et al.* (15), insulin levels were also significantly elevated compared with the insulin-sensitive group, leaving the possibility that here also high insulin levels may have been responsible for the observed mitochondrial aberrations. However, Heilbronn *et al.* (15) added a second part to their study, in which they exercise-trained their subjects for 6 wk with four 40-min sessions per week, adding up to some 3 h of exercise per week. Both the insulin-sensitive and insulin-resistant groups significantly improved their insulin sensitivity and aerobic fitness, but no changes in mitochondrial proteins were detected. The lack of an effect on mitochondrial metabolism may, however, be owing to the power of the study because strong significant correlations were observed between the change in aerobic fitness and/or insulin sensitivity and the protein content of complex III/V of the mitochondrial electron transport chain. Although these correlations could indicate that the exercise-induced enhancement of insulin sensitivity improved mitochondrial metabolism, this is not very likely given the well-known potent and direct stimulatory effects of endurance training on mitochondrial biogenesis (18). Therefore, the strong relation between the change in protein content of mitochondrial complex III/V and insulin sensitivity most likely should be interpreted as a positive effect of improved mitochondrial biogenesis/content on insulin sensitivity.

Does this imply that we can conclude that mitochondrial abnormalities lead to type 2 diabetes mellitus? Obviously, many more, valuable human intervention studies like this one are required to definitely answer this question. For example, it will be valuable to investigate the effect of interventions with well-characterized insulin-sensitizing properties acting via nonmitochondrial pathways on mitochondrial metabolism. Such intervention studies can further unravel if mitochondrial abnormalities are the cause or consequence of the insulin-resistant state. In addition, studies are urgently needed that will pinpoint the exact location of the mitochondrial abnormalities, if any. So far, the available data that favor a role for mitochondria in the etiology of muscular insulin resistance have used a wide range of methodologies and techniques to study mitochondrial "metabolism." These methodologies range from the simple determination of mitochondrial gene transcripts, mitochondrial protein and DNA content, enzyme activities, and *ex vivo* mitochondrial function in isolated mitochondria to noninvasive measurement of mitochondrial oxidative capacity. All these methodologies address different aspects of mitochondrial metabolism, like mitochondrial biogenesis, mitochondrial density, and mitochondrial function, and the results may be confounded by factors like muscle fiber type and blood flow/perfusion. Therefore, multifaceted studies examining all of the above-mentioned aspects in relation to insulin sensitivity are needed. Regardless of the outcome of these studies, we must hope that the renewed interest for mitochondria in the research field of type 2 diabetes mellitus will also further vitalize the promotional and financial actions needed by government and other public parties to stimulate further physical activity in the fight against the diabetic epidemic. If anything, the papers of Heilbronn *et al.* (15) and many others before unquestionably show the potency of physical exercise training to overcome insulin resistance.

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